Latent tuberculosis infection in rural China: baseline results of a population-based, multicentre, prospective cohort study

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Summary

Background Prophylactic treatment of individuals with latent *Mycobacterium tuberculosis* infection is an essential component of tuberculosis control in some settings. In China, the prevalence of latent tuberculosis infection, and preventive interventions against this disease, have not been systematically studied. We aimed to assess the prevalence of latent tuberculosis and its associated risk factors in rural populations in China.

Methods Between July 1, and Sept 30, 2013, we undertook a baseline survey of a population-based, multicentre, prospective cohort study of registered residents (≥5 years old) at four study sites in rural China. Eligible participants were identified by door-to-door survey with a household sampling design. We screened participants for active tuberculosis and history of tuberculosis then used a tuberculin skin test and an interferon-γ release assay (QuantiFERON [QFT]) to test for latent infection. We used odds ratios (ORs) and 95% CIs to assess variables associated with positivity of QFT and tuberculin skin tests.

Findings 21 022 (90%) of 23 483 eligible participants completed a baseline survey. Age-standardised and sex-standardised rates of skin-test positivity (≥10 mm) ranged from 15% to 42%, and QFT positivity rates ranged from 13% to 20%. Rates of positivity for the tuberculin skin test and the QFT test were low in study participants younger than 20 years and gradually increased with age (p for trend <0·0001). Rates of latent tuberculosis infection were higher for men than women (p<0·0001). Overall agreement between the tuberculin skin test and the QFT test was moderate (81·06%; kappa coefficient 0·485), with skin-test-only positive results associated with the presence of BCG scar, male sex, and ages of 60 years and older, and QFT-only positive results associated with male sex and ages of 60 years and older.

Interpretation On the basis of findings showing that the performance of the tuberculin skin test might be affected by various factors including BCG vaccination and age, our results suggest that the prevalence of latent tuberculosis in China might be overestimated by skin tests compared with interferon-γ release assays.

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Introduction

Almost 20 years after WHO declared tuberculosis a global public health emergency, the infection remains a major global health problem. Despite substantial progress to combat this disease, an estimated 8·6 million incident cases were recorded in 2012, and the rate of decline is slow at 2% per year.[1] In 2012, China had the second largest number of incident cases worldwide (0·9 million to 1·1 million), accounting for 12% of the global total. China's 2013 National Tuberculosis Prevention and Control Management guidelines emphasised the strategy of treatment as prevention to improve tuberculosis control.[2]

Neonatal BCG vaccination has been ongoing in China since the 1950s and was included in the national immunisation system in 1978, but protection is insufficient in various populations.[3] Such low levels of protection might be related to the vaccine's effectiveness or the absence of complete coverage in these populations. As such, identification and treatment of latent tuberculosis infection in individuals at high risk of developing active disease has been practiced as an effective strategy for tuberculosis control in some countries, such as the USA. An estimated 5–10% of people with latent tuberculosis will develop active disease, and treatment of latent infection alone could prevent 64% of incident cases in WHOs Southeast Asia Region.[4] Before a national strategy for treatment of latent tuberculosis can be developed, policy makers should have an understanding of the local epidemiology and whether there is a basis for development of a community wide intervention to prevent active tuberculosis by treatment of latent infection.[5] However, population-based data for the prevalence of latent tuberculosis and the risk of progression to active disease are not available in China.

In China, about 71% of patients with tuberculosis live in rural areas.[6–8] Therefore, we assessed registered residents of different rural areas in China to identify the groups in

whom latent tuberculosis is most prevalent, and to assess the risk of development of active disease in those infected.

Methods

Study design and participants

Between July 1, and Sept 30, 2013, we undertook a baseline survey of an ongoing population-based, multicentre, prospective cohort study of registered residents at four study sites in rural China. The cohort study, which was organised by the Institute of Pathogen Biology of Chinese Academy of Medical Sciences and the Chinese Center for Disease Control and Prevention (CDC), has two phases, encompassing 3 years (2013–15; appendix). In phase 1 of the baseline survey, we screened participants for active tuberculosis and history of tuberculosis, then tested for latent infection after exclusion of those with present tuberculosis or a history of the disease. In the follow-up phase (phase 2, which is presently underway), we will follow up participants in whom we detected latent tuberculosis at baseline for development of active disease. The sample was stratified by study site (A, B, C, or D), which we selected on the basis of a wide range of local tuberculosis epidemiology, economic conditions, and geographical locations.

Eligible participants were identified by door-to-door survey. Inclusion criteria were birth before June 1, 2008 (≥5 years old); household registration or residence permit for that village; continuous residence at the study site for 6 months or longer in the past year;[6] ability to complete the investigations and tests during the study duration; and provision of voluntary written informed consent. Exclusion criteria were present active tuberculosis, self-reported history of tuberculosis, and pregnancy.

The study protocol was approved by the ethics committee of the Institute of Pathogen Biology, Chinese Academy of Medical Sciences (Beijing, China). All participants, or legal guardians of participants if necessary, provided written informed consent.

Procedures

Because there is no gold-standard test to diagnose latent tuberculosis, we used an interferon-γ release assay (QuantiFERON-TB Gold In-Tube [QFT; Qiagen; Valencia, CA, USA]) in parallel with the tuberculin skin test to test each participant. By contrast with the skin test, interferon-γ release assay are unaffected by previous BCG vaccination or exposure to most non-tuberculous mycobacteria.[9,10]

We took measures to guarantee data quality and comparability between the four study sites, including standardisation of study protocol and standard operating procedures, standardised training of research staff, use of reagents with the same batch number, and standardised laboratory materials and equipment. Study staff from all four sites completed four rounds of centralised training (around 300 person-times) on clinical examinations, laboratory procedures and questionnaire investigations Additionally, we designated trained staff with responsibility for internal quality control to assess the accuracy and reproducibility of the key procedures and tests during study implementation. Westat (Rockville, MD, USA) provided independent site monitoring (external quality assessment), according to the procedures and requirements of the study protocol.

For each study participant, trained interviewers collected sociodemographic information by use of a standardised questionnaire. Data obtained included that for ethnic origin, educational level, occupation, marital status, household income per head in 2012 (ie, total family income/number of people in the household), area of household living space, and smoking and alcohol consumption status. We also assessed present status of tuberculosis infection and history of reported tuberculosis disease, history of close contact with a patient with tuberculosis, history of immune suppression, and chronic diseases. We verified information about history of present and previous tuberculosis with the national active tuberculosis case report system. Physicians obtained and assessed symptoms of suspected pulmonary tuberculosis. Physicians also examined height, weight, pulse, and presence of a BCG scar. Blood biochemical examinations were provided for free to encourage participation.

We regarded age, sex, occupation, and educational level as demographic factors in the analyses. On the basis of previous reports, history of contact with patients with tuberculosis, history of immune system disorders, smoking and alcohol drinking status, household income per head, body-mass index (BMI; calculated), and number of BCG scars were classified as potential factors associated with infection risks. We classified household income per head on the basis of the national mean level in 2010 (6000 RMB).[11] We categorised BMI as underweight (<18·5 kg/m²), normal weight (≥18·5 kg/m² to <24·0 kg/m²), overweight (≥24·0 kg/m² to 28·0 kg/m²), or obese (≥28·0 kg/m²).[12]

Venous blood was collected for QFT. QFT testing was done as recommended by the manufacturer, with a cutoff value of 0·35 IU/mL or more. Tuberculin skin testing was done immediately after the QFT test and used the Mantoux method—ie, injection of 0·1 mL of 5 tuberculin units of purified protein derivative (Xiangrui; Beijing, China) intradermally into the left forearm as a preference.[13] Trained study personnel measured tuberculin reaction size (induration) in mm after 48–72 h of placement. Participants with evidence of skin disease on their forearms did not undergo tuberculin skin tests. Digital chest radiography was done in all participants older than 15 years , and in those younger than 15 years with reported suspected symptoms of pulmonary tuberculosis or history of close contacts.

Participants with symptoms of pulmonary tuberculosis or with radiographic abnormalities consistent with active pulmonary disease were transferred to the local city level CDC for disease confirmation, in accordance with WHO guidelines. Individuals with sputum-smear-positive or

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See **Online** for appendix

culture-positive pulmonary tuberculosis, or with suspected pulmonary infection (defined by radiographic abnormalities consistent with active pulmonary infection together with a positive QFT test or a strong positive tuberculin skin test [induration ≥15 mm or presence of blister or necrosis]) were not included in the analysis of latent tuberculosis.

Statistical analysis

The baseline survey followed a household sampling design. Registered households were randomly selected by probability proportional to sample size. Sample size for the cohort study was established for differences in incidence of active tuberculosis between patients exposed and unexposed to latent tuberculosis (appendix). The minimum sample size required at baseline was 22 000 participants (5500 participants at each site).[14,15] Questionnaire data, physical examination data (height, weight, pulse, presence of BCG scar, and tuberculin skin test), and laboratory results (QFT and blood biochemical examination) were double entered into a spreadsheet and checked by web-based project-specific data collection and management software (LATENTTB-NSTM data management system [version 1.2]). After cleaning, the data were converted and analysed with SAS (version 9.2).

We compared the frequency of categorical variables in participants between the study sites with Pearson's χ^2 test. To identify potential variables related to positivity of QFT and tuberculin skin tests, we did univariate analysis with Pearson's χ^2 test. All variables with p values less than 0·05 in univariate analysis were entered into the unconditional multiple logistic regression analyses and the associations assessed with odds ratios (OR) and 95% CIs. For different cutoff values of the tuberculin skin test, we calculated the corresponding Cohen's kappa coefficient to assess the agreement between QFT and tuberculin skin tests.[16]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows detailed information about the study sites and the population assessed. We selected sites with a range of tuberculosis incidence (table 1). Of 23 438 eligible participants, 21 832 actually participated, with a response rate of 93%. After exclusion of 2416 (10%) participants, 21 022 participants were included in the final analysis (table 1).

Overall, roughly half of participants were female and almost a quarter were 60 years or older (table 2). Sex and age distributions differed significantly across sites (table 2). Participants from site A had higher educational levels and household incomes per head than did those from the other three sites (table 2). A quarter of participants reported having ever smoked and about a

	Site A	Site B	Site C	Site D	Total
Geographical location	Eastern China, plains	Central China, plains	Western China, hills	Western China, basin	NA
Mean income per head in 2012 (RMB)	14 396	11 326	7800	4427	NA
Proportion of migrant worker population in 2012	10%	5%	24%	12%	NA
Reported incidence of active tuberculosis in 2010 (per 100 000 population)	53·5	91·3	105·6	81·9	NA
Registered population established by cluster sampling*	8735 (23%)	7470 (20%)	10 131 (27%)	11 128 (30%)	37 464
Excluded because not defined as resident population	1424 (14%)	816 (8%)	3434 (34%)	4555 (43%)	10 229
Excluded because <5 years old	110 (6%)	680 (40%)	531 (31%)	386 (23%)	1707
Excluded because of pregnancy	4 (4%)	35 (36%)	32 (33%)	25 (26%)	96
Excluded because of present active pulmonary tuberculosis	0	8 (30%)	13 (48%)	6 (22%)	27
Excluded because declined to participate or could not complete study period	1199 (61%)	120 (6%)	225 (11%)	423 (22%)	1967
Eligible population included in the baseline survey	5998 (26%)	5811 (25%)	5896 (25%)	5733 (24%)	23 438
Excluded because did not participate in baseline survey despite having signed consent	520 (32%)	425 (26%)	455 (28%)	206 (13%)	1606
Excluded because of absent result from interferon-γ release assay	2 (25%)	0	3 (38%)	3 (38%)	8
Excluded because of absent results from digital chest radiography	38 (37%)	10 (10%)	23 (23%)	31 (30%)	102
Excluded because of self-reported history of tuberculosis	45 (12%)	42 (11%)	232 (63%)	47 (13%)	366
Excluded because of present clinically suspected pulmonary tuberculosis†	29 (9%)	45 (13%)	202 (60%)	58 (17%)	334
Actual population assessed for the prevalence of latent tuberculosis infection	5364 (26%)	5289 (25%)	4981 (24%)	5388 (26%)	21 022

Data are n (%), unless otherwise indicated. Sum of percentages might not always total 100% because of rounding. NA=not available. *Registered residents identified by door-to-door survey. †If digital chest radiography abnormal and results for interferon-γ release assays were positive or tuberculin skin tests were strong positive (ie, induration diameter ≥15 mm or presence of blister or necrosis), we classified cases as having clinically suspected pulmonary tuberculosis.

Table 1: **Population sampling among the study sites**

	Total (N=21 022)	Site A (n=5464)	Site B (n=5289)	Site C (n=4981)	Site D (n=5388)	p for χ^2 test
Sex						<0·0001
Female	11 286 (54%)	2862 (53%)	2605 (49%)	2694 (54%)	3125 (58%)	..
Male	9736 (46%)	2502 (47%)	2684 (51%)	2287 (46%)	2263 (42%)	..
Age (years)						<0·0001
5–9	1459 (7%)	90 (2%)	620 (12%)	232 (5%)	517 (10%)	..
10–19	2100 (10%)	275 (5%)	537 (10%)	390 (8%)	898 (17%)	..
20–29	2058 (10%)	403 (7%)	771 (15%)	344 (7%)	540 (10%)	..
30–39	2183 (10%)	456 (8%)	566 (11%)	443 (9%)	718 (13%)	..
40–49	4651 (22%)	1260 (23%)	1161 (22%)	1084 (22%)	1146 (21%)	..
50–59	3613 (17%)	1174 (22%)	746 (14%)	1009 (20%)	684 (13%)	..
60–69	3136 (15%)	1069 (20%)	539 (10%)	944 (19%)	584 (11%)	..
≥70	1822 (9%)	637 (12%)	349 (7%)	535 (11%)	301 (6%)	..
Highest education level						<0·0001
Primary school or lower	11 175 (53%)	2405 (45%)	2892 (55%)	2749 (55%)	3129 (58%)	..
Middle school	6888 (33%)	2102 (39%)	1680 (32%)	1692 (34%)	1414 (26%)	..
High school	2305 (11%)	667 (12%)	530 (10%)	453 (9%)	655 (12%)	..
College or higher	654 (3%)	190 (3%)	187 (3%)	87 (2%)	190 (3%)	..
Household per capita income (RMB)						<0·0001
<6000	13 418 (64%)	1373 (25%)	4433 (84%)	3124 (63%)	4488 (83%)	..
≥6000	7603 (36%)	3991 (74%)	855 (16%)	1857 (37%)	900 (17%)	..
Smoking status						<0·0001
Never smoked	15 812 (75%)	4049 (75%)	3932 (74%)	3441 (69%)	4390 (82%)	..
Ever smoked	5207 (25%)	1315 (24%)	1354 (26%)	1540 (31%)	998 (18%)	..
Alcohol drinking						<0·0001
No	17 027 (81%)	4167 (78%)	3894 (74%)	4172 (84%)	4794 (89%)	..
Yes	3994 (19%)	1197 (22%)	1394 (26%)	809 (16%)	594 (11%)	..
BMI (kg/m^2)						<0·0001
<18·5	10 092 (48%)	2922 (54%)	2076 (39%)	2523 (51%)	2571 (48%)	..
≥18·5–<24	3278 (16%)	347 (6%)	906 (17%)	714 (14%)	1311 (24%)	..
≥24–<28	5599 (27%)	1648 (31%)	1447 (27%)	1302 (26%)	1202 (22%)	..
≥28	2052 (10%)	447 (8%)	860 (16%)	441 (9%)	304 (6%)	..
Number of BCG scars						<0·0001
0	10 383 (49%)	3466 (65%)	1051 (20%)	1101 (22%)	4765 (88%)	..
1	7060 (34%)	1457 (27%)	2288 (43%)	2702 (54%)	613 (11%)	..
≥2	3577 (17%)	440 (8%)	1950 (37%)	1177 (24%)	10 (<1%)	..
History of close contact with patient with tuberculosis						<0·0001
No	19 228 (95%)	5248 (99%)	5071 (97%)	4101 (87%)	4808 (99%)	..
Yes	913 (4%)	77 (1%)	178 (3%)	620 (13%)	38 (1%)	..
TST induration (mm)						<0·0001
<5	12 673 (60%)	2991 (56%)	3175 (60%)	2316 (47%)	4191 (78%)	..
5–9	2428 (12%)	369 (7%)	1318 (25%)	520 (10%)	221 (4%)	..
10–14	1857 (9%)	627 (12%)	397 (7%)	564 (11%)	269 (5%)	..
≥15	4021 (19%)	1368 (25%)	394 (7%)	1554 (31%)	705 (13%)	..
QFT test						<0·0001
Negative	16 467 (78%)	4252 (79%)	4379 (83%)	3591 (72%)	4245 (70%)	..
Positive	3955 (19%)	1056 (20%)	821 (15%)	1198 (24%)	880 (16%)	..
Indeterminate	600 (3%)	56 (1%)	89 (2%)	192 (4%)	263 (5%)	..

Data are n (%), unless otherwise indicated. Sum might not always be in total because of missing data. Frequency off missing data did not differ significantly between sites. BMI=body-mass index. TST=tuberculin skin test. QFT=QuantiFERON-TB Gold In-Tube.

Table 2: **Baseline characteristics and the prevalence of TST and QFT**

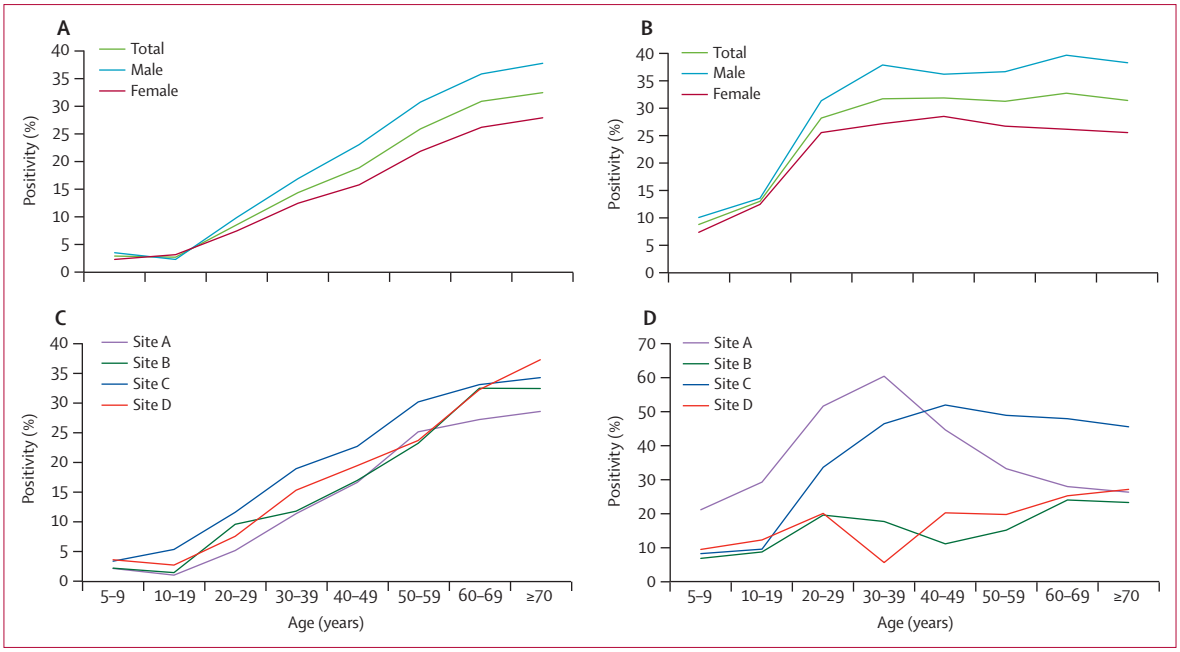

***Figure 1*: Prevalence of QFT and TST (≥10 mm) positivity by age and sex (A, B) and age and study site (C, D)**
QFT=QuantiFERON-TB Gold In-Tube. TST=tuberculin skin test.

fifth had ever consumed alcohol (table 2). BMI distribution showed that more than a third of the participants were overweight or obese (table 2). Half of participants had a BCG scar (table 2).

43 (<1%) participants had missing data for the tuberculin skin test either because the test was not done or because the result was not read during the valid time. The appendix has detailed information about results of the QFT and tuberculin skin tests by age and study site. In total, 8306 (40%) of 20 985 participants had an induration of 5 mm or more, 5878 (28%) participants had an induration of 10 mm or more, and 4021 (19%) had an induration of 15 mm or more (table 2). Overall, 19% of participants were QFT positive and 3% tests gave an indeterminate result (table 2). Men were more likely than women to have positive results by both tuberculin skin test and QFT (figure 1). We noted an increasing trend for QFT positivity with increasing age for both men and women (p for trend <0·0001). By contrast with results of the skin test, positive QFT results continued to increase with age, with no sign of plateauing (figure 1). The distribution of QFT positivity by age between the study sites was similar, but we noted varied distributions for positivity of tuberculin skin tests across the sites (figure 1). For site A, the groups with the most positive results for tuberculin skin-test (≥10 mm) positivity were aged 20–49 years. After standardisation for age and sex, site A had the highest result for skin-test positivity, but the lowest QFT positivity and prevalence of confirmed and suspected pulmonary tuberculosis (figure 2).

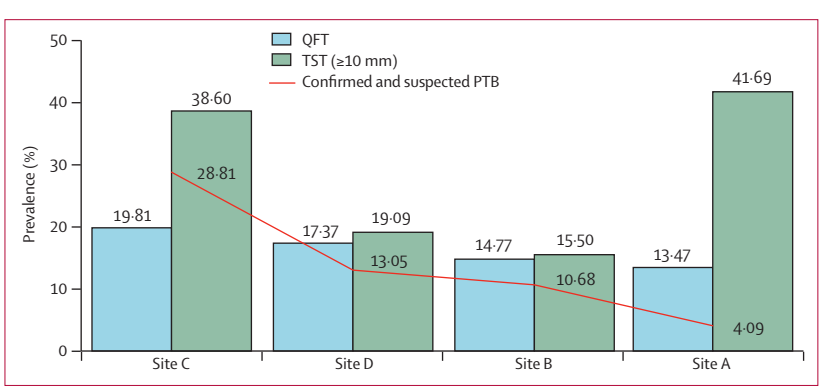

***Figure 2*: Age-standardised and sex-standardised prevalence of QFT positivity, TST (≥10 mm) positivity, and confirmed and suspected PTB, by study site**
Prevalence for QFT and TST is per 100 people, and for confirmed and suspected PTB is per 1000 people. QFT=QuantiFERON-TB Gold In-Tube. TST=tuberculin skin test. PTB=pulmonary tuberculosis.

Factors significantly associated with tuberculin skin-test positivity were male sex, increasing age, middle-school and high-school education (compared with primary school education), family income of 6000 RMB or more, history of smoking, consumption of alcohol, presence of BCG scar, a BMI of less than 18·5 kg/m², and history of close contact with a patient with tuberculosis (table 3). For QFT positivity, we noted that male sex and ages of 20 years or older were associated with positive results, as were a history of smoking, close contact with a patient with tuberculosis, and a BMI of 28 kg/m² or more (table 3).

Agreement between the tuberculin skin test and QFT was only moderate, with 16 520 (81%) of the 20 380 participants with valid results showing concordance and a kappa coefficient of 0·485 (95% CI 0·471–0·498). We recorded the highest correlation between QFT and the tuberculin skin test when we increased the cutoff value of the skin test to 14 mm

(appendix). The level of the agreement between QFT and the tuberculin skin test, and the best agreement cutoff values for the skin test, varied between the sites, according to estimations of the kappa coefficient (appendix).

2933 (51%) of 5780 participants who had positive tuberculin skin tests also had positive QFT tests, whereas 2933 (74%) of the 3946 participants who were QFT positive were also skin-test positive (appendix). 442 (74%) of 599 participants with an intermediate QFT result had a skin-test response of less than 5 mm (appendix). Table 4 shows results of the analysis of discordance between the tuberculin skin test and the QFT test. Skin-test-only positive results were significantly associated with male sex, ages of 60 years and older, and BCG vaccination after controlling for age and sex, whereas QFT-only positive results were associated with male sex and old age (≥60 years), but not BCG vaccination, after controlling for sex and BCG vaccination (table 4). Agreement between the tuberculin skin test and QFT was higher in participants without a BCG scar than in those with a scar in participants younger than 50 years; however, for participants aged 50 years and older, we recorded a similar level of agreement

	TST (≥10 mm)			QFT positivity		
	n (%)	p for χ^2 test	Adjusted OR* (95% CI)	n (%)	p for χ^2 test	Adjusted OR* (95% CI)
Sex		<0·0001			<0·0001	
Female	2761/11 269 (24%)	..	Reference	1832/11 286 (16%)	..	Reference
Male	3117/9710 (32%)	..	1·25 (1·14–1·36)	2123/9736 (22%)	..	1·27 (1·14–1·41)
Age (years)		<0·0001			<0·0001	
5–9	129/1457 (9%)	..	Reference	43/1459 (3%)	..	Reference
10–19	274/2096 (13%)	..	1·30 (1·02–1·65)	57/2100 (3%)	..	0·76 (0·50–1·16)
20–29	579/2051 (28%)	..	2·85 (2·22–3·67)	176/2058 (8%)	..	2·23 (1·51–3·27)
30–39	691/2179 (32%)	..	3·72 (2·90–4·76)	313/2183 (14%)	..	3·96 (2·74–5·74)
40–49	1481/4641 (32%)	..	3·91 (3·08– 4·96)	876/4651 (19%)	..	5·35 (3·75–7·64)
50–59	1127/3606 (32%)	..	3·78 (2·98–4·80)	934/3613 (26%)	..	8·13 (5·70–11·60)
60–69	1025/3131 (33%)	..	4·57 (3·61–5·80)	966/3136 (31%)	..	10·69 (7·52–15·20)
≥70	572/1818 (31%)	..	4·79 (3·76–6·11)	590/1822 (32%)	..	11·90 (8·35–16·97)
Education level		<0·0001			<0·0001	
Primary school or lower	2737/11 159 (24%)	..	Reference	2236/11 175 (20%)	..	Reference
Middle school	2217/6868 (32%)	..	1·24 (1·15–1·34)	1276/6888 (18%)	..	1·08 (0·98–1·18)
High school	722/2300 (31%)	..	1·31 (1·17–1·47)	375/2305 (16%)	..	1·10 (0·95–1·26)
College or higher	202/652 (31%)	..	1·33 (1·09–1·62)	68/654 (10%)	..	1·00 (0·75–1·33)
Family income per head (RMB)		<0·0001			<0·0001	
<6000	3231/13 396 (24%)	..	Reference	2513/13 418 (19%)	..	Reference
≥6000	2647/7582 (35%)	..	1·56 (1·46–1·67)	1442/7603 (19%)	..	0·97 (0·90–1·05)
Smoking status		<0·0001			<0·0001	
Never smoked	3830/15 789 (24%)	..	Reference	2486/15 812 (16%)	..	Reference
Ever smoked	2048/5187 (39%)	..	1·59 (1·44–1·75)	1469/5207 (28%)	..	1·35 (1·21–1·50)
Alcohol drinking		<0·0001			<0·0001	
No	4558/16 998 (27%)	..	Reference	2958/17 027 (17%)	..	Reference
Yes	1320/3980 (33%)	..	0·72 (0·65–0·79)	997/3994 (25%)	..	0·95 (0·86–1·05)
Number of BCG scars		<0·0001			<0·0001	
0	2516/10 364 (24%)	..	Reference	2055/10 383 (20%)	..	Reference
1	2227/7040 (32%)	..	1·76 (1·63–1·90)	1094/7060 (15%)	..	0·99 (0·91–1·08)
≥2	1135/3573 (32%)	..	1·33 (1·21–1·45)	806/3577 (22%)	..	1·03 (0·93–1·14)
BMI (kg/m^2)		<0·0001			<0·0001	
<18·5	3004/10 073 (30%)	..	0·84 (0·73–0·97)	2003/10 092 (20%)	..	0·84 (0·70–1·00)
≥18·5–<24	481/3271 (15%)	..	Reference	230/3278 (7%)	..	Reference
≥24–<28	1774/5584 (32%)	..	1·04 (0·97–1·13)	1257/5599 (22%)	..	1·08 (0·99–1·17)
≥28	618/2050 (30%)	..	0·97 (0·87–1·08)	465/2052 (23%)	..	1·15 (1·02–1·30)
History of close contact with patient with tuberculosis		<0·0001			<0·0001	
No	5245/19 188 (27%)	..	Reference	3526/19 228 (18%)	..	Reference
Yes	360/910 (40%)	..	1·49 (1·29–1·72)	250/913 (27%)	..	1·55 (1·32–1·81)

Data are n (%), unless otherwise indicated. TST=tuberculin skin test. OR=odds ratio. QFT=QuantiFERON-TB Gold In-Tube. BMI=body-mass index. *Controlling for variables with p<0·05 in univariate analysis.

Table 3: **Univariate and multivariate analysis of TST and QFT positivity**

between the two tests (with ≥10 mm as the skin-test cutoff) in patients with and without a BCG scar (figure 3).

Discussion

Results for both QFT and tuberculin skin tests were associated with sex, age, BMI, history of smoking, and history of close contact with patients with tuberculosis. The effect of age and BCG vaccination on the tuberculin skin test might explain the discordance between these two methods. Therefore, our results suggest that the presently estimated rates of latent tuberculosis in endemic regions of China have probably been overestimated by the tuberculin skin test compared with interferon-γ release assays.

In the past few decades, China has made substantial progress in tackling the tuberculosis epidemic,[7,8] nevertheless, it still has the second largest number of incident cases of all countries worldwide. In addition to further strengthening of treatment success rates nationwide, integration of prevention with control efforts and decreasing of the incidence of active tuberculosis are national strategies for tuberculosis control. Prophylactic treatment of latent infection has been suggested and practised in China as an important component of tuberculosis prevention, but has been restricted to close contacts of patients with tuberculosis and those with possible HIV and tuberculosis co-infection.[2] In developed countries where tuberculosis incidence has fallen to fairly low levels, treatment of people with latent infection is a major component of tuberculosis control because this group represent an enormous reservoir for tuberculosis transmission.[17] However, the situation has historically been

	TST-/QFT-	TST+/QFT+	TST-/QFT+	TST+/QFT-	Adjusted OR* (95%CI)		
					TST+/QFT+ *vs* TST-/QFT-	TST-/QFT+ *vs* TST-/QFT-	TST+/QFT- *vs* TST-/QFT -
Total	13 587 (67%)	2933 (14%)	1013 (5%)	2945 (14%)	..	..	..
Sex							
Female	8013 (71%)	1332 (12%)	495 (4%)	1429 (13%)	Reference	Reference	Reference
Male	6075 (63%)	1601 (16%)	518 (5%)	1516 (16%)	1·58 (1·46–1·72)	1·41 (1·24–1·60)	1·35 (1·25–1·46)
Age (years)							
<60 years	11 181 (70%)	1826 (11%)	568 (3%)	2455 (15%)	Reference	Reference	Reference
≥60 years	2907 (59%)	1107 (22%)	445 (9%)	490 (10%)	2·38 (2·18–2·59)	3·01 (2·64–3·44)	0·85 (0·76–0·95)
BCG scar							
Absent	7280 (70%)	1482 (14%)	568 (4%)	1034 (10%)	Reference	Reference	Reference
Present	6807 (64%)	1451 (14%)	445 (4%)	1911 (18%)	1·12 (1·04–1·22)	0·95 (0·84–1·09)	1·91 (1·76–2·08)
Age / BCG scar							
<60 years/BCG-	5424 (73%)	881 (12%)	275 (4%)	798 (11%)	Reference	Reference	Reference
<60 years/BCG+	5757 (66%)	945 (12%)	293 (3%)	1657 (19%)	0·98 (0·89–1·09)	0·98 (0·83–1·16)	1·92 (1·75–2·11)
≥60 years/BCG-	1856 (62%)	601 (20%)	293 (10%)	236 (8%)	1·98 (1·77–2·23)	3·11 (2·61–3·69)	0·86 (0·74–1·01)
≥60 years/BCG+	1050 (53%)	506 (26%)	152 (8%)	254 (13%)	2·91 (2·56–3·31)	2·83 (2·30–3·49)	1·62 (1·38–1·89)

Data are n (%), unless otherwise indicated. TST=tuberculin skin test. QFT=QuantiFERON-TB Gold In-Tube. OR=odds ratio. *Adjusted for sex, age, and status of BCG scar.

Table 4: **Multivariate analysis of discordance between QFT and TST (≥10 mm)**

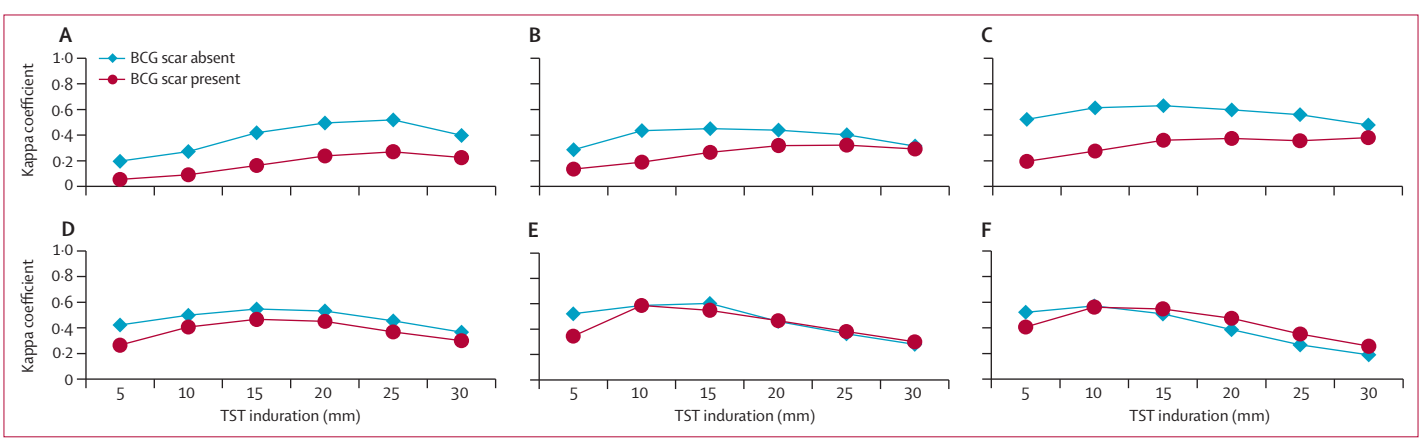

Figure 3: **Agreement between QFT and TST according to TST cutoff values by age and BCG vaccination status**

Age groups were younger than 20 years (A), 20–29 years (B), 30–39 years (C), 40–49 years (D), 50–59 years (E), and 60 years and older (F). The agreement between QFT and TST when using different TST cutoff values was assessed with Cohen's kappa test. TST=tuberculin skin test. QFT=QuantiFERON-TB Gold In-Tube.

different in countries with a high burden of tuberculosis, and detection and treatment of latent infection has not been recommended. This absence of focus towards prevention was based on many factors, but one belief was that because there might be constant exposure to *M tuberculosis* in such countries, individuals treated would just be re-exposed and reinfected. Nevertheless, such speculation should be based on academic or scientific data and should take the present local public health situation into consideration.

The present study represents a first step in China to address the important topic of development of tuberculosis control strategies (panel). In 2000, findings from the fourth National Tuberculosis Epidemiology survey showed that the rate of *M tuberculosis* infection (defined by a tuberculin skin-test response ≥6 mm) was 44·5% for all age groups in China.[14] Now, popular opinion is that half the Chinese population are infected with *M tuberculosis*. With the availability of interferon-γ release assays, the prevalence of latent tuberculosis infection has been investigated in specific populations in China, such as in new army recruits,[18] students,[19] and health-care workers.[20] However, the sample sizes of such studies were quite small. Our findings, for the first time, provide important evidence showing that in the general population with a range of active tuberculosis rates, the size of target populations with latent infection (for preventive intervention) might not be as large as previously imagined.

Findings from our subgroup analysis showed that QFT positivity was significantly associated with the absence of BCG scar in participants younger than 20 years but not in older participants. One interpretation of this finding could be that although BCG vaccination does have protective efficacy in the first few years after immunisation, any protection diminishes with time. BCG vaccination was included in the national immunisation programme in China since 1978; therefore, poor coverage of vaccination in individuals born before that time might also explain the poor effect of BCG vaccine in adults in this study population. Additionally, by contrast with the increasing rates of QFT positivity in adolescent populations in high-burden settings such as South Africa,[21] QFT positivity rates in participants in our study did not start to increase until age 20–29 years. We noted this trend across all four sites and recorded similar trends for the tuberculin skin test. This finding could be due to the few exposure opportunities for rural children. However, the potential protective effect of BCG vaccination in children and adolescents, but not in adults, cannot be excluded.[22,23] Our data provide further evidence to support the view that BCG vaccination has little or no protective role for tuberculosis control in adults. On the basis of evidence suggesting that BCG vaccination does not confer protection in adults, and the basic observation that most people in China who develop active tuberculosis are BCG vaccinated, it is clear that other tuberculosis control measures are needed.[24,25] Screening of high-risk populations for latent tuberculosis infection with interferon-γ release assays, and provision of preventive treatment for those testing positive and with high risks of developing disease, would be an important strategy to decease tuberculosis incidence.

After standardisation for age and sex, we recorded variation between the study sites in results for both tuberculin skin tests and QFT tests. The rate of QFT positivity at each study site was consistent with the corresponding prevalence rate of clinically suspected pulmonary tuberculosis; however, such consistency was not shown for the tuberculin skin test. Our results suggest that the geographical diversity of latent tuberculosis prevalence as measured by QFT is in line with local tuberculosis rates. Such geographical diversity should be considered during the design of monitoring and intervention strategies for latent tuberculosis.

Association analyses in the present study suggest that results for both tuberculin skin tests (≥10 mm) and QFT tests are somehow related to sex, age, smoking history, BMI, and history of close contact with patients with tuberculosis. However, the reported ORs might overestimate the true risk ratio when the positivity rates were higher than 10%.[26] In rural areas, women almost always work in agriculture and in the home, and do not have as many exposure opportunities as men, who have more active social responsibilities. The trend of increasing QFT positivity with increasing age is probably related to the accumulation of exposure opportunities. We noted a significant association between smoking history and prevalence of latent tuberculosis in our study population. This association has been reported in various other populations.[27] A proposed underlying biological

***Panel*: Research in context**

Systematic review

We searched PubMed for articles published in English up to Nov 26, 2014, with the search terms "latent tuberculosis infection" OR "latent" AND "tuberculosis" and "China". Of the 112 articles we identified, 14 were meta-analysis or review and 77 did not epidemiologically investigate latent tuberculosis infection in mainland China. Of the 21 eligible reports, five were done in health-care workers, five in patients accepting anti-tumour necrosis factor-α therapy, four in BCG-vaccinated participants, three in military recruits, two in individuals who had been in close contact with patients with active tuberculosis, and two in students. No population-based multicentre study addressing latent tuberculosis infection in rural China was identified.

Interpretation

Our large-scale, multicentre prospective study is the first to investigate the epidemiology of latent tuberculosis infection in China with use of the tuberculin skin test and an interferon-γ release assay. Here we reported the results of the baseline survey of this study. On the basis of evidence showing that the performance of the tuberculin skin test might be affected by various factors including BCG vaccination and age, our results suggest that the prevalence of latent tuberculosis infection in China might be overestimated by tuberculin skin tests compared with interferon-γ release assays. As a result, testing of high-risk populations and prophylactic treatment of individuals with latent tuberculosis infection might be feasible at the community level in China. Such an approach could be of great benefit to China's national tuberculosis control strategy.

mechanism is that alveolar macrophages from smokers might be less successful in controlling intracellular *M tuberculosis* than are those from never smokers.[28,29] As a result, tuberculosis control policies should incorporate tobacco control as a preventive intervention.

Close contacts of patients with tuberculosis, elderly people, and smokers might be potential target populations for monitoring of latent tuberculosis with preventive interventions because of the increased risk of prevalence of latent infection in these populations. Contact investigations and active case finding among close contacts of patients with active tuberculosis have been a regular part of tuberculosis control in China, but such work has not been done in elderly people and smokers.

In the present study, results of tuberculin skin tests were affected by several factors including old age and the status of BCG vaccination. The best agreement between the skin test and the QFT test varied from a skin-test cutoff of about 15 mm for 40 year olds to a cutoff of 10 mm for people older than 60 years. Additionally, skin-test positivity tended to plateau after middle-age, which might show that sensitivity of the test reduces with increasing age. This decline could be due to difficulties in application of the skin test to ageing skin or the inability of elderly skin to react.[24] BCG vaccination can produce false positives on tuberculin skin tests, and such a positive relation between the presence of BCG scar and skin-test positivity was shown in our study. Additionally, results of tuberculin skin tests can also be affected by exposure to non-tuberculosis mycobacteria. Skin-test positivity peaked at middle age at site A. This finding cannot be explained by inaccurate measurement of the skin-test result; rather, BCG vaccination and non-tuberculosis mycobacterial infection might be the most likely explanations. Site A is located in the coastal region of east China—a region in which we postulate residents might have increased exposure to non-tuberculosis mycobacteria. However, we have little epidemiological evidence about non-tuberculosis mycobacteria to support this hypothesis. We will assess this topic during the follow-up phase of this study. In summary, caution is warranted in interpretation of results of tuberculin skin tests in individuals who are BCG vaccinated, elderly, and reside in regions where non-tuberculosis mycobacteria is prevalent. Interferon-γ release assays might provide more solid information than tuberculin skin tests about latent infection in such high-risk populations.

This study is not without its limitations. First, because many individuals in the 20–40-year-old age group were not resident at their registered household, our study population is not representative of the general population in China. However, we feel we have aptly described the rural population in China because adults in this age group generally move from rural areas to urban areas to find employment. Differences in demographic characteristics across the study sites are not surprising in view of the differences in migratory nature of the adult working population at these geographically diverse sites. Second, interferon-γ release assays as a class of immune-based diagnostic test have not been extensively validated in China. In this study, we used a standard cutoff of 0·35 IU/mL for the QFT test, which might not be the most appropriate cutoff for this study population. Furthermore, the appropriate cutoff for the tuberculin skin test might need to take age and BCG vaccination status into consideration. Therefore, dichotomous cutoff for the QFT and tuberculin skin tests might be inadequate for interpretation.[30] Our group is undertaking further analyses of cutoff values for both tests. The rate of indeterminate QFT test results (3%) across all age groups in our study is consistent with the indeterminate rate in a meta-analysis[31] of 21922 participants in 72 QFT studies (2%). Further analysis of our findings showed that 73% of participants with indeterminate QFT results had an induration of less than 5 mm with the tuberculin skin test and 83% of those had indurations of less than 10 mm, which suggests that many of the indeterminate QFT results might be due to depressed immune status.

Despite these limitations, our results provide valuable insight into the prevalence of latent tuberculosis infection in countries with a high burden, but medium incidence, of tuberculosis where BCG vaccination is routinely given. Specifically for China, our results suggest that the rate of latent infection is not as high as previously described. This finding suggests that community-based preventive interventions to control disease development from latent tuberculosis might be practical for individuals at high risk for developing active diseases.

Contributors

Q J designed the study. LG, YZ, and SC implemented the study. WL, LB, JW, and XJ organised investigations at the study sites. XL, YY, ML, BF, ZL, HX, HW, JD, HS were responsible for quality control of baseline investigation at the study sites. RZ, XL, YY, and YX did data management and quality control. JL, SP, FS, JH, SY, HS, YW, ZX, YT, TC, HP, ZW, TZ, and WX enrolled study participants and did baseline investigations and tests. LG, XL, YY, WL, LB, JW, XJ, FZ, CA, and CV analysed data and wrote the report. Q J, YZ, SC, HL, XC, FZ, CA, CV, and XZ commented on the report. All authors contributed to review and revision and have seen and approved the final version of the manuscript.

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Declaration of interests

We declare no competing interests.

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